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Opioid agonist treatment for pharmaceutical opioid dependent people (Protocol)

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Opioid agonist treatment for pharmaceutical opioid dependent people (Protocol)

Abstract

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: To assess the effects of maintenance agonist pharmacotherapy treatments for the treatment of pharmaceutical opioid dependence.

Keywords

pharmaceutical, dependent, treatment, opioid, agonist, (protocol), people

Disciplines

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Opioid agonist treatment for pharmaceutical opioid dependent people

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of maintenance agonist pharmacotherapy treatments for the treatment of pharmaceutical opioid dependence.

BACKGROUND

Description of the condition

The misuse of pharmaceutical drugs has been described as a major health problem. An estimated 26 to 36 million people were using opioids in 2010, with around half using pharmaceutical opioids (UNODC 2012). There are an estimated 15.6 million opioid-dependent people worldwide, with the global consumption of opioids considered to be increasing (WHO 2009). Opioid dependence is a chronic relapsing condition with significant cost to human life (Hser 2001; Grella 2011).

Dependence upon pharmaceutical opioids has been well established as a problem in the United States of America (USA) and Canada (Fischer 2012; Manchikanti 2012). In the USA, pharmaceutical opioids are reported to be increasingly used by young people, and pain medications are second to marijuana as the drug used by new illicit drug initiates (NSDUH 2011).

Globally, illicit opioid use is a major cause of mortality from both acute effects of intoxication (e.g. overdose and traffic accidents) and transmission of blood-borne disease associated with injection drug use (such as human immunodeficiency virus (HIV) and hepatitis C) (Degenhardt 2009). In the USA, where pharmaceutical opioid use has been described as an epidemic, pharmaceutical opioid overdose is one of the leading cause of mortality, with deaths from pharmaceutical opioids exceeding the number of deaths from heroin and cocaine (Paulozzi 2006). In the USA in 2007, more people died from prescription opioid overdose than motor vehicle accidents and suicides (Manchikanti 2012). Similarly high rates of pharmaceutical opioid use have been described in Canada (Fischer 2012). Although other countries are yet to reach the magnitude of the problems seen in the USA and Canada, there is evidence of increased pharmaceutical opioid use and harms. A global review identified that pharmaceutical opioid diversion, non-medical use and injection was a considerable problem in the USA, South Asia, South East Asia and some European countries (Degenhardt 2007).

In Europe, non-medical use of prescription opioids is documented, including the problematic use of non-prescription codeine in the United Kingdom (UK) and France. An estimated 1.6% to 1.7 % of the German population are thought to be dependent on prescription drugs (Casati 2012). Increasing treatment presentations with prescription and over-the-counter codeine opioids are reported in South Africa (Myers 2003), where five to eight per cent of treatment presentations are now associated with over-the-counter opioid dependence (Weich 2008). Increasing reports of use and harms with pharmaceutical opioids are also reported in Australia, with increasing mortality due to oxycodone, and increasing hospital presentations for pharmaceutical opioids including over-the-counter codeine (Frei 2010; Rintoul 2010; Roxburgh 2011). The number of hospital poisonings in Australia from pharmaceutical opioids exceeded heroin in 2004 and has continued to grow every year, and the number of treatment episodes for oxycodone doubled over a five-year period, though it still only represent a fraction of the treatment episodes for heroin dependence (Roxburgh 2011).

Description of the intervention

Opioid agonist treatments are established to be effective in the treatment of heroin dependence (Clark 2002; Faggiano 2003; Mattick 2009; Mattick 2014). The two main opioid agonist treatments that are widely available are methadone and buprenorphine. Methadone is well established as a treatment and has a strong evidence base demonstrating its effectiveness in reducing mortality and substance use, improving physical and mental health outcomes, reducing criminal activity, and reducing HIV risk and risk behaviours (Caplehorn 1996; Amato 2005; Gowing 2011; Mattick 2014). Methadone is a synthetic μ -opioid agonist, and an N-methyl-D-aspartate (NMDA) antagonist. It has a half-life of 24 to 36 hours and has close to 100% oral bioavailability. Methadone is generally given as a single daily dose in the treatment of opioid dependence. Methadone doses of 60 to 100 mg have been demonstrated to be more effective in retaining people in treatment compared with lower doses (Faggiano 2003).

Buprenorphine is a partial opioid agonist, having a lower intrinsic activity at the opioid receptor, but due to its high affinity for the opioid receptor, being able to act as an antagonist blocking the effect of other opioids. Buprenorphine has a favourable safety profile due to its ceiling on respiratory effects (Walsh 1994), with mortality in treatment appearing to be relatively less common with buprenorphine compared with methadone in naturalistic study designs in Australia and France (Auriacombe 2001; Degenhardt 2009). Buprenorphine has poor oral bioavailability, and is available in sublingual formulations for the treatment of opioid dependence. Due to its pharmacological properties, buprenorphine is able to be given as larger doses every second or third day (Amass 2000). Levo-alpha-acetylmethadol (LAAM) was concluded to be more effective than methadone for reducing heroin use (Clark 2002),

but it is currently not commercially available. Other therapies such as slow release oral morphine have also been explored.

How the intervention might work

Opioid agonist treatment, also known as opioid substitution treatment involves prescribing maintenance dose of an opioid medication in place of the drug of dependence. Most of the original research done into opioid substitution treatment involved prescribing a legal opioid such as methadone or buprenorphine in place of an illicit opioid such as heroin. The provision of a regular dose of a legal and medically sanctioned opioid treatment enables a reduction in illicit or unsanctioned opioids use, with associated improvement health and social stability. The dose of the substitution medication is adjusted to a level that prevents withdrawal without causing sedation. Regular dosing maintains a fairly constant blood level, so that the sense of euphoria or intoxication usually associated with each dose of the drug (either illicit or prescribed) is lessened. Substitution treatment decreases the frequency and intensity of the cycle of intoxication and withdrawal, allowing the client to better address the associated issues necessary for recovery. Psychosocial support provided in conjunction with medication addresses the psychological health and social environment of the opioid user and helps to improve both the quality and duration of life (WHO 2009).

Opioid agonist treatment works by provision of a regular dose of μ opioid agonist that bind at the μ opioid receptor, alleviating opioid withdrawal symptoms. Providing a stable dose of opioid agonist has been demonstrated to lead to numerous health and social benefits for opioid dependent people, specifically though reducing illicit opioid use (Amato 2005; Mattick 2009; Mattick 2014), HIV risk behaviour (Gowing 2011), HIV seroconversion (MacArthur 2012) and criminality (Amato 2005; Mattick 2009). It has been proven to improve physical and mental health, and social functioning (Padaiga 2007; Mattick 2009; Mattick 2014) and reduce mortality (Degenhardt 2011).

Why it is important to do this review

Opioid agonist treatment is commonly initiated as a first-line treatment for individuals with pharmaceutical opioid dependence, even though much of the evidence base for the use of pharmacotherapy treatments in opioid dependence has been derived from studies conducted with primarily or exclusively heroin-dependent samples. Users of pharmaceutical opioids (i.e. both prescription opioids and over-the-counter opioids such as codeine) have been described in the literature to be a different patient population with a number of characteristics that differ from heroin-using populations, including having a higher prevalence of physical and mental health co-morbidities.

Prescription opioid dependence has been described to be at epidemic levels in the USA and has been reported to be increasing globally. Establishing an evidence base for treatment of prescription opioid dependence is therefore timely and critical. An emerging evidence base exists for the use of opioid agonist treatments in prescription opioid dependence, but a systematic review is yet to be conducted to determine whether similar outcomes can be expected for this new population of opioid dependent people. This review will fill an evidence gap informing clinicians about effective approaches using agonist pharmacotherapies for pharmaceutical opioid dependence.

OBJECTIVES

To assess the effects of maintenance agonist pharmacotherapy treatments for the treatment of pharmaceutical opioid dependence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs)

Types of participants

People who have been assessed by study staff to meet DSM IV, ICD-10, or other validated criteria for pharmaceutical opioid dependence, or have been assessed by a clinician to meet criteria for pharmaceutical opioid dependence (i.e. a population meeting criteria for 'addiction' rather than just physiological neuro-adaptation in the absence of other behaviours suggesting dependence). Pharmaceutical opioid dependent people will not include those who are currently taking pharmaceutical opioids in the context of opioid substitution treatment. Where participants have been reported to be 'opioid dependent', as opposed to specifically dependent on pharmaceutical opioids, the main opioid used prior to treatment entry must have been a pharmaceutical opioid. We will exclude studies examining opioid treatments primarily for pain and not for the treatment of opioid dependence.

Where study populations are not exclusively comprised of primary pharmaceutical opioid dependent people, at least 80% of the study participants must have reported pharmaceutical opioids as their primary substance to be included in the analysis. Where subpopulations of pharmaceutical opioid users do not meet 80% of the study, population data will be requested for sub-analysis,

with only participants meeting the above criteria included in the analysis. We will contact study authors where necessary to confirm levels of use of pharmaceutical opioids.

Types of interventions

Maintenance opioid agonist treatments, where maintenance is defined as at least 30 days of opioid agonist treatment. We will include trials that have made the following comparisons:

1. Full opioid agonists (methadone, morphine, oxycodone, LAAM or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment
2. Full or partial opioid agonist maintenance versus placebo, detoxification only or psychological treatment (without opioid agonist treatment)

Types of outcome measures

Outcome measures will not be considered as part of the eligibility criteria.

Primary outcomes

1. Days of unsanctioned opioid use at the end of the intervention period
2. Per cent abstinent at treatment completion (self report and with urine drug screen)
3. Retention

Secondary outcomes

1. Pain, assessed by validated scales such as the Brief Pain Inventory (Cleland 1991) and the McGill Pain Questionnaire (Melzack 1975).
2. Risk behaviours (injecting, sexual, polydrug use, overdoses or hospital admissions)
3. Adverse effects (participants experiencing any adverse event, or serious adverse event)
4. Aberrant opioid related behaviours (e.g. seeing multiple doctors for extra opioid medication, lost medication, unauthorised dose escalations)
5. Employment
6. Quality of life, as assessed by validated scales such as the SF-36 (Ware 1992) and the WHO QoL or WHOQoL-BREF (WHO 1997)
7. Physical health, as assessed by validated scales such as the SF-36 (Ware 1992)
8. Psychological health, as assessed by validated scales such as the SF-36 (Ware 1992), K10 (Kessler 2002), or the DASS (Lovibond 1995)

Outcomes can be self reported or objectively measured.

Search methods for identification of studies

Electronic searches

A search strategy was developed in consultation with a drug and alcohol research information specialist, and search terms revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

We will search:

1. Cochrane Drugs and Alcohol Group's Specialised Register of Trials;
2. The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, most recent issue);
3. PubMed (January 1966 to present);
4. EMBASE (Ovid) (January 1974 to present);
5. CINAHL (EbscoHOST) (1982 to present);
6. ISI Web of Science;
7. PsycINFO (Ovid).

Searching other resources

We will search abstract databases including the National Institute on Drug Abuse/College on Problems of Drug Dependence (NIDA/CPDD) abstracts, as well as clinical trial registers.

We will search the reference lists of all relevant papers to identify further studies, in addition to contacting the authors of all included studies to enquire if there are other relevant published or unpublished studies. All searches will include English and non-English language literature. Studies with non-English language abstracts will be assessed for inclusion.

Data collection and analysis

Selection of studies

One review author will inspect the titles and abstracts identified by the above searches. The full text of each potentially relevant article will be requested, and two review authors will then assess the studies independently for inclusion. Where the two authors are not able to reach agreement following their independent review of the full text, a third author will assess the studies to assist in reaching consensus.

Data extraction and management

Data will be extracted independently by two review authors using a data collection form, with a third author involved where there is disagreement between the two authors to assist in reaching consensus.

Information about the number of participants treated, drug and dosing regimen, study design, study duration and follow-up, and

outcomes listed at including pain, substance use outcome measures, treatment retention, risk behaviors, employment, quality of life, physical and psychological health, and adverse events (participants experiencing any adverse event, or serious adverse event) will be extracted from each study and recorded on a data extraction sheet.

We will attempt to collect and utilise the most detailed numerical data that might facilitate similar analyses of included studies. Where 2×2 tables or means and standard deviations are not available, effect estimates (e.g. odds ratios, regression coefficients), confidence intervals, test statistics (e.g. *t*, *F*, *Z*, *Chi*²) or *P* values, or data from individual participants may be used in the analyses (see also [Measures of treatment effect](#)).

Assessment of risk of bias in included studies

The risk of bias assessment for RCTs in this review will be performed using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). This comprises a two-part tool addressing seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments we will use the criteria indicated by the *Cochrane Handbook* ([Higgins 2011](#)), adapted to the addiction field. See [Appendix 2](#) for details.

The domains of sequence generation and allocation concealment (avoidance of selection bias) will be addressed in the tool by a single entry for each study.

Blinding of participants, personnel and outcome assessor (avoidance of performance bias and detection bias) will be considered separately for objective outcomes (e.g. drop out, use of substance of abuse measured by urine analysis, subjects relapsed at the end of follow up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance, side effects, social functioning as integration at school or at work, family relationship).

Incomplete outcome data (avoidance of attrition bias) will be considered for all outcomes except for the drop out from the treatment, which is often the primary outcome measure in trials on addiction.

Measures of treatment effect

Where possible, the treatment effect for each dichotomous outcome will be expressed as a relative risk (RR) with 95% confidence

intervals (CI). Where there is a comparable consistent outcome measure (e.g. time in treatment) the treatment effect for each continuous outcome will be expressed as a mean difference (MD) with 95% CIs. Where there is variability in outcome measure (e.g. quality of life scales, risk behavior measures or pain scales) the treatment effect for each continuous outcome will be expressed as a standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

If there are trials with multiple treatment arms that may be included in a meta-analysis, then we will either combine groups to allow single-pair wise comparisons or we will set up separate analyses or perform subgroup analyses and suppress the calculation of overall totals to avoid the unit of analysis error of double-counting participants.

Dealing with missing data

Where data are missing we will contact the original investigators to request missing data, and will attempt to determine if data are missing at random or if missing data are associated with a different outcome to that for which data are available (for example, where outcome data are unavailable due to participant drop-out). Sensitivity analysis will be conducted to determine this (as per section 9.7 *Cochrane Handbook* (Higgins 2011)). Where there appears to be an important amount of missing data, the possible effects of the missing data on the review will be described in the Discussion section.

Assessment of heterogeneity

We will consider clinical heterogeneity (variability in the participants, interventions and outcomes studied) and methodological heterogeneity (variability in study design and risk of bias).

Meta-analysis will be considered if a group of studies are sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary. Where this is not the case, and the heterogeneity of the included studies precludes a meta-analysis being performed, the relevant studies will be described separately.

To assess heterogeneity, initially we will inspect the results graphically. A P value of the test lower than 0.10 or an I^2 statistic of at least 50% will indicate significant statistical heterogeneity.

Assessment of reporting biases

If a meta-analysis is conducted, funnel plots (plots of the effect estimate from each study against the standard error) will be used to assess the potential for bias related to the size of the trials, which could indicate possible publication bias.

When there appears to be selective outcome reporting, we will contact the study authors to request additional information.

Data synthesis

Key findings of studies will first be summarised descriptively before considering if studies are appropriate for quantitative meta-analysis. We will contact study authors if we require additional information to enable inclusion of studies in meta-analyses.

Statistical analysis will be undertaken using Review Manager 5 software (RevMan 2012).

The outcomes of the individual trials will be combined through meta-analysis where possible (depending on the comparability of interventions and outcomes between trials) with the use of a random-effects model, as some variability is expected in the included studies. Where meta-analysis is not possible a narrative synthesis of the findings will be reported.

Subgroup analysis and investigation of heterogeneity

If sufficient studies are included in the review, the following subgroups of participants will be examined and investigated for potential sources of heterogeneity:

- With and without chronic pain
- With and without a history of heroin use
- With and without a history of injecting drug use
- With and without mental health problems

Sensitivity analysis

Where the effect of a decision on the outcome of the review is uncertain (for example, the decision to include or exclude a study remains unclear, or the impact of unavailable data on the findings is uncertain), sensitivity analysis will be conducted, with the results described in a summary table (see *Cochrane Handbook* section 9.7 (Higgins 2011)).

To incorporate risk of bias assessment in the review process we will first plot intervention effect estimates for different outcomes stratified for risk of bias for each item. If differences in results are present among studies at different risk of bias, we will perform sensitivity analysis, excluding studies at a high risk of bias. We will also perform subgroup analysis for studies at a low and unclear risk of bias.

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- * Indicates the major publication for the study

APPENDICES

Appendix 1. PubMed search strategy

1. "Opioid-Related Disorders"[MeSH]
2. ((opiate*[tiab] OR opioid*[tiab] OR morphin*[tiab] OR morfin*[tiab] OR narcot*[tiab]) AND (abuse*[tiab] OR abusing[tiab] OR addict*[tiab] OR misus*[tiab] OR depend*[tiab] OR disorder*[tiab]))
3. #1 OR #2
4. "Analgesics, Opioid"[MeSH]
5. "Narcotics"[MeSH]
6. ((opioid*[tiab] OR opiat*[tiab]) AND analges*[tiab])
7. "Prescription Drugs"[MeSH]
8. ((prescript*[tiab] OR prescrib*[tiab] OR pharmaceutical[tiab]) AND (opioid*[tiab] OR opiate*[tiab]))
9. #4 OR #5 OR #6 OR #7 OR #8
10. randomized controlled trial [pt]
11. controlled clinical trial [pt]
12. randomized [tiab]
13. placebo [tiab]
14. drug therapy [sh]
15. randomly [tiab]
16. trial [tiab]
17. groups [tiab]
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19. animals [mh] NOT humans [mh]
20. #18NOT #19
21. #3 AND #9 AND #20

Appendix 2. Criteria for risk of bias assessment

Item	Judgment	Description
1. random sequence generation (selection bias)	low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation
	high risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. allocation concealment (selection bias)	low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and phar-

(Continued)

		macy-controlled, randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes
	high risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. blinding of participants and providers (performance bias) Objective outcomes	low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	high risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	unclear risk	Insufficient information to permit judgement of low or high risk
4. blinding of participants and providers (performance bias) Subjective outcomes	low risk	Blinding of participants and providers and unlikely that the blinding could have been broken
	high risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	unclear risk	Insufficient information to permit judgement of low or high risk;
5. blinding of outcome assessor (detection bias) Objective outcomes	low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken

(Continued)

	high risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	unclear risk	Insufficient information to permit judgement of low or high risk;
6.blinding of outcome assessor (detection bias) Subjective outcomes	low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	high risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	unclear risk	Insufficient information to permit judgement of low or high risk
7. incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically-relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically-relevant impact on observed effect size; Missing data have been imputed using appropriate methods; All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	high risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically-relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

(Continued)

	unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group)
8 selective reporting (reporting bias)	low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	high risk	Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	unclear risk	Insufficient information to permit judgement of low or high risk

CONTRIBUTIONS OF AUTHORS

Draft the protocol	Nielsen, Degenhardt, Lintzeris, Gowing, Lintzeris
Develop and run the search strategy	Nielsen, Larance, Degenhardt, Kehler
Obtain copies of studies	Kehler, Larance, Nielsen
Select which studies to include (2 people)	Nielsen, Degenhardt, Lintzeris, Gowing, Larance
Extract data from studies (2 people)	Nielsen, Degenhardt, Lintzeris, Gowing, Larance
Enter data into RevMan	Nielsen, Kehler
Carry out the analysis	Nielsen, Allsop, Degenhardt
Interpret the analysis	Nielsen, Larance, Degenhardt, Lintzeris, Gowing
Draft the final review	Nielsen, Larance, Degenhardt, Lintzeris, Gowing

(Continued)

Update the review	Nielsen, Larance, Degenhardt, Lintzeris, Gowing
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DECLARATIONS OF INTEREST

Suzanne Nielsen, Louisa Degenhardt, Briony Larance and Nicholas Lintzeris have previously been investigators on research projects funded by untied educational grants from Reckitt Benckiser. That company has no role in the conception of, or decision to submit, this protocol and have no role in the review. Suzanne Nielsen and Louisa Degenhardt are funded by an NHMRC fellowship. The NHMRC has no interest in the outcome of the review that could lead to a real or perceived conflict of interest.

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